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TRIAZOLAM - PERFORMANCE SIDE EFFECTS: VESTIBULAR, MUSCULOSKELETAL, AND COMPLEX PERFORMANCE TESTS

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PENSACOLA, FLORIDA

Volunteer subjects were recruited, evaluated, and employed in accordance with the procedures specified in Department of Defense Directive 3216.2 and Secretary of the Navy Instruction 3900.39 series. These instructions are based upon voluntary informed consent and meet or exceed the provisions of prevailing national and international guidelines.

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Transient insomnia preceding or during intense military aviation operations has, in some cases, been treated by short-acting benzodiazepines like temazepam or triazolam. This study evaluated selected physiological and performance side effects of triazolam (0.25 mg) administered to nine men and one woman. Each subject completed drug and placebo testing, which started at one and eight hours following drug administration. Testing included measures of balance, fine motor movement, two-dimensional tracking, tilt table, tri-service performance assessment battery, pulmonary function, bike ergometer, and strength/endurance. This dose of triazolam produced no significant change in any of the tests with the exception of the balance tests ($p < .05$). This study did not identify any significant performance side effects that would disqualify this agent for acute short-term use against insomnia sometimes encountered in the military aviation environment.

Keywords: Sleep deprivation; Aerospace medicine

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SUMMARY PAGE

THE PROBLEM

Transient insomnia preceding or during intense military aviation operations has, in some cases, been treated by short-acting benzodiazepines like temazepam or triazolam. The objective of this test sequence was to evaluate the effect of triazolam on aviator performance and flight safety using a series of tests focusing on vestibular, musculoskeletal, and complex performance.

FINDINGS

This study evaluated selected physiological and performance side effects of triazolam (0.25 mg) administered to nine men and one woman. Testing was initiated at 1 and 8 hours following drug administration, and included measures of balance, fine motor movement, two-dimensional tracking, tilt table, tri-service performance assessment battery, pulmonary function, cardiovascular endurance, and musculoskeletal strength/endurance. This dose of triazolam (0.25 mg) produced no significant change in any of the tests with the exception of the balance tests ($p < .05$).

RECOMMENDATIONS

We recommend: (1) a more sensitive balance test be used in future investigations; (2) potential changes in psychological and vision functions be explored; (3) future studies should include control drug(s) to confirm test sensitivity; (4) before using this agent in an operational scenario, aviators should be screened by a drug challenge to identify any idiosyncratic reactions; and (5) additional research on dose-response effects be conducted. Within the confines of our test battery, we did not identify any significant performance side effects that would disqualify 0.25 mg triazolam for acute/short-term use against insomnia sometimes encountered in the military aviation environment.

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Volunteer subjects were recruited, evaluated, and employed in accordance with the procedures specified in Department of Defense Directive 3216.2 and Secretary of the Navy Instruction 3900.39 series. These instructions are based upon voluntary informed consent and meet or exceed the provisions of prevailing national and international guidelines.

PREFACE

Aviation safety and operational readiness are of the highest priority for aviation commanders and flight surgeons. Medical conditions and treatment that impact flight safety complicate this priority. In many cases, the illness itself is sufficient reason to preclude safe flight, thus, the aviator is grounded until the illness is resolved. In other cases, medical conditions may not necessarily adversely affect performance, but their treatment gives rise to questions regarding the effect of therapeutic agents on the aviator's performance in the highly complex arena of flight.

At the present time, decisions to allow flight while under treatment are made on the basis of experience accumulated by senior aerospace medicine specialists. Use of some drugs for minor illness is left to the discretion of the operational flight surgeon. Longer term drug therapies are permitted on a case-by-case basis with a waiver. The performance effects of certain drugs, i.e., alcohol, are amply described in aviation-related literature. Aviation-relevant information on other pharmaceuticals, however, is either meager or non-existent.

The purpose of this project was to evaluate the effects of drugs identified by the Aeromedical Advisory Council and others on aviator performance and flight safety. The initial sequence of tests focuses on potential performance side effects associated with the drug triazolam. This paper describes results from selected vestibular, musculoskeletal, and complex performance tests.

INTRODUCTION

Insomnia preceding and during intense military aviation operations has, in some cases, been treated by short-acting benzodiazepines. Therapeutically, these agents should induce rapid sleep onset, provide good quality sleep, be rapidly eliminated, and have no residual after effects. The intent of this pharmacological intervention is to improve or maintain the aviator's performance by avoiding sleep deprivation preceding the mission. During the South Atlantic Campaign, the Royal Air Force successfully used temazepam, whereas in the United States, much attention has focused on a related compound, triazolam.

Triazolam has a half-life of from 1.5 to 3.8 h (19,23,30,38,42). It is effective for rapid sleep induction and increased sleep duration without the attendant loss of morning alertness (2,6,7,8,10,11,13,15,16,20,21,25, 28,29,41,45,46,48,50,51,57,65,69,74,75). Discontinuation after repeated administration can result in rebound insomnia (1,44,49,79) although some reports dispute this finding (64,81). The literature is divided on the presence of physiological or psychological side effects, which might impair performance. Research indicating that triazolam has either minimal or no side effects (6,10,11,12,34,47,52,53,55,56,60,63,67,74,76,82) should be considered in relation to other articles indicating performance impairment (6,9,14,26,27,35,36,37,39,40,43,45,54,55,68,71,73,77,80,81,83,85,87), which in some cases persisted into the next day.

This report explores several areas of potential impairment: strength/endurance (18,84), manual dexterity (61), tracking and cognitive performance (37,39,41,81,82), and balance. Balance or vestibular side effects have been suggested by reports of vertigo (22,27), dizziness (68), disorientation (24), ataxia (40,86), and nausea or vomiting (66,71).

PROCEDURE

SUBJECTS

The 10 subjects (9 men and 1 woman) who participated in this study were a mixture of laboratory personnel and student naval flight officers awaiting assignment. All subjects passed a physical exam and participated on a voluntary basis.

DRUG

A double-blind procedure was used for the oral administration of either 0.25 mg triazolam or a placebo of roughly the same size.

BRIEF DESCRIPTION OF TESTS

1. Balance. Two tests from the 'Floor Ataxia Test Battery' were used to evaluate potential changes in balance. The two tests were: Sharpened Romberg (SR: standing heel-to-toe, Fig. 1) and Walk-on-Floor-Eyes-Closed (WOFEC: walking heel-to-toe, Fig. 2). Testing and scoring procedures are described in previous reports (31,32,33).

Fig. 1. The Sharpened Romberg is a static test of equilibrium performed with eyes closed, arms folded across the chest, and feet in a non-moving tandem position.

Fig. 2. The Walk-on-Floor-Eyes-Closed (WOFEC) test is an ambulatory test of equilibrium similar to the Sharpened Romberg, but requiring ten steps to be made by the subject.

2. Interval Production Task (58,59). The interval production task required subjects to generate a series of time intervals by tapping a finger key at a rate of one to three responses per second. The goal of the task was to maintain equal time intervals by tapping at as regular a rate as possible. The task was administered using two 3-min trials with a 1-min rest between trials. Intervals were timed from the onset of one response to the onset of the next response with intervals of less than 10 ms rejected as spurious input. The subject tapped with the forefinger of the preferred hand and simultaneously performed a mental arithmetic task.

3. Matrix Rotation Test (17,70). A series of 5 x 5 cell matrices were presented (one at a time in the center of the CRT), with five illuminated cells per matrix (Fig. 3). The subject compared successive displays and determined if they were the "same" or "different" from the immediately preceding matrix. Following each response, a new matrix was presented, and the subject again decided if it was the same or different from the immediately preceding matrix. Responses required pressing one key for "same" and another key for "different." A matrix could be identical to the preceding matrix in two ways: either exactly the same cells were illuminated, but the matrix was rotated 90° to the left; or exactly the same cells were illuminated, but the matrix was rotated 90° to the right. Two successive matrices were never presented in exactly the same orientation. The testing session consisted of twelve 1-min trials with a 15-s break between trials.

4. Tilt Table Test. A classic tilt table procedure (Fig. 4) was used to measure orthostatically induced changes in blood pressure (BP) and heart rate (HR), which were recorded every 60 s during a 5-min supine, 15-min at 20 deg. off-vertical, and 5-min supine testing sequence.

5. Pegboard Tests. A pegboard test was used to evaluate coordinated fine motor movement capability (Fig. 5). The dependent measure for this test was time to correctly place 25 pegs. Performance using left and right hands was tested separately.

6. Tracking. Two-dimensional compensatory tracking of a laser-projected artificial horizon (Fig. 6) was used as a measure of coordinated fine motor control. Tracking abilility (rms) was evaluated using four artificial horizon sizes (visual angles of 3.9°, 9°, 16°, 30°). The testing session consisted of four 4-min trials (one for each horizon size) with 1.5-min rest periods between trials.

7. Submaximal Working Capacity Test (Bicycle Ergometer). An Astrand Multi-Stage test (4) for physical working capacity at 150 beats per minute (PWC_{150}) was utilized (Fig. 7). Maximum oxygen uptake per minute (VO_2 max) was predicted from the steady state heart rate and workload prior to the 150 bpm cutoff heart rate.

8. Muscle Strength and Endurance. Dynamic strength and endurance were measured using the Cybex II Isokinetic Muscle Tension Testing Equipment (Fig. 8). Peak strength (knee flexion and extension) was measured at a speed of 60° per second during five maximal repetitions. Muscular endurance was measured at 180° per second during 50 repetitions. Mean force-output decline provided endurance information. Performance measures were: work performed in five repetitions (Joules), average power (watts), muscle tension intensity measured in peak torque (Newton-meters), peak torque

Fig. 3. The matrix rotation task measures both spatial orientation and short-term memory.

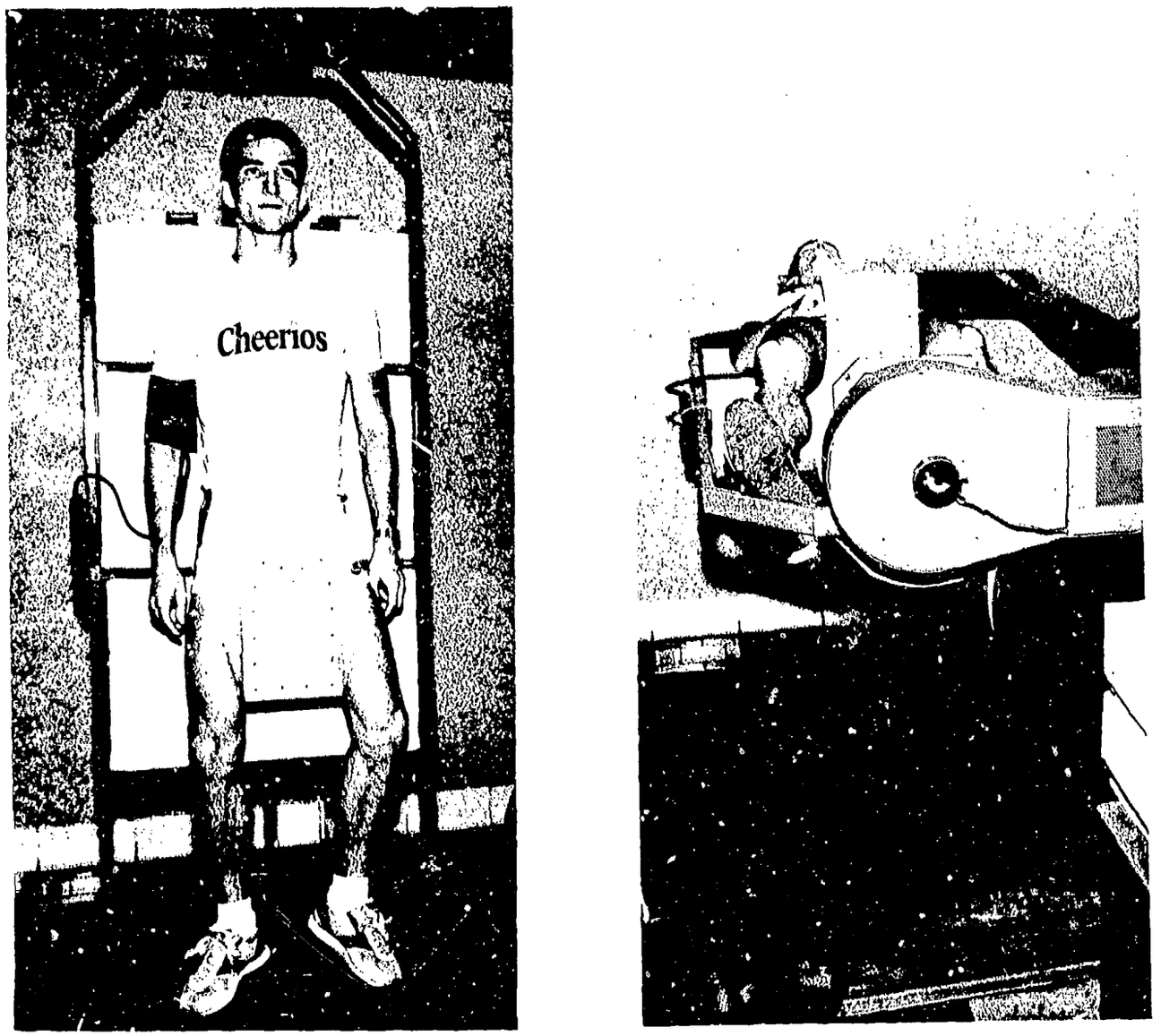

Fig. 4. A classic tilt table procedure was used to measure orthostatically induced changes of blood pressure and heart rate.

Fig. 5. The classic pegboard test is a simple measure of coordinated fine motor movement.

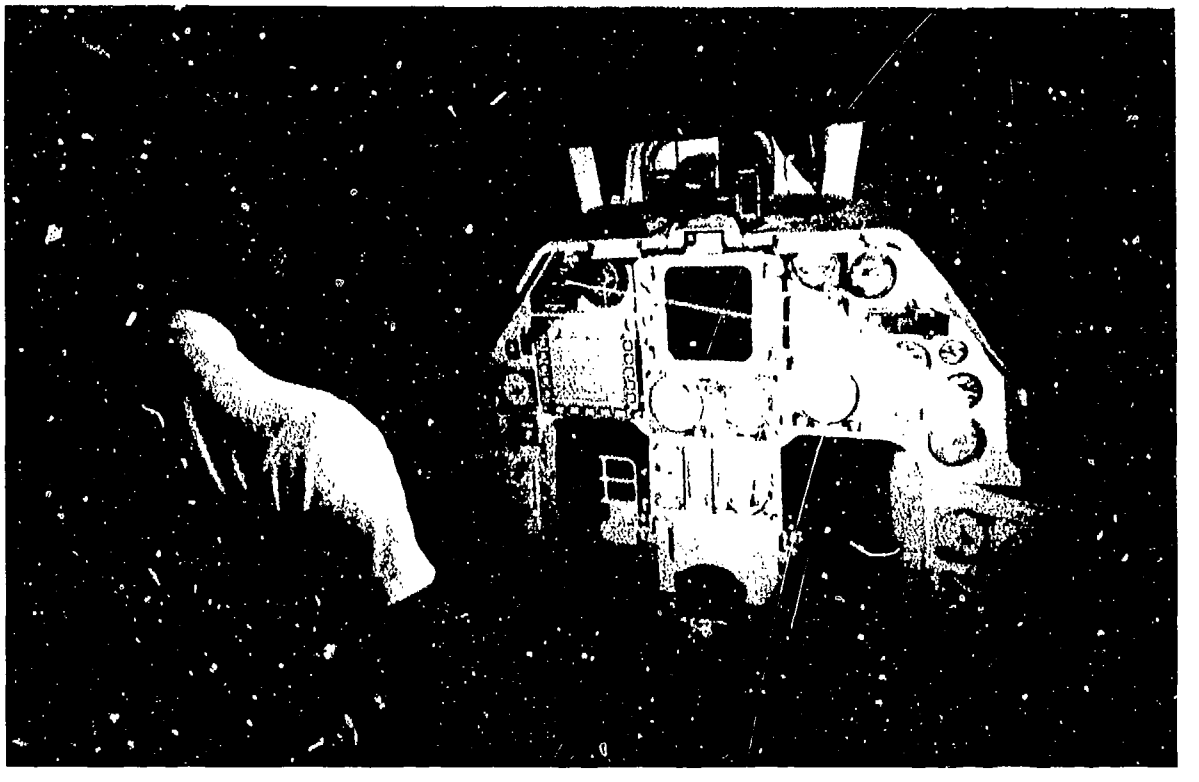

Fig. 6. The two-dimensional tracking task uses a laser-projected horizon and measures fine motor movement combined with limited information processing.

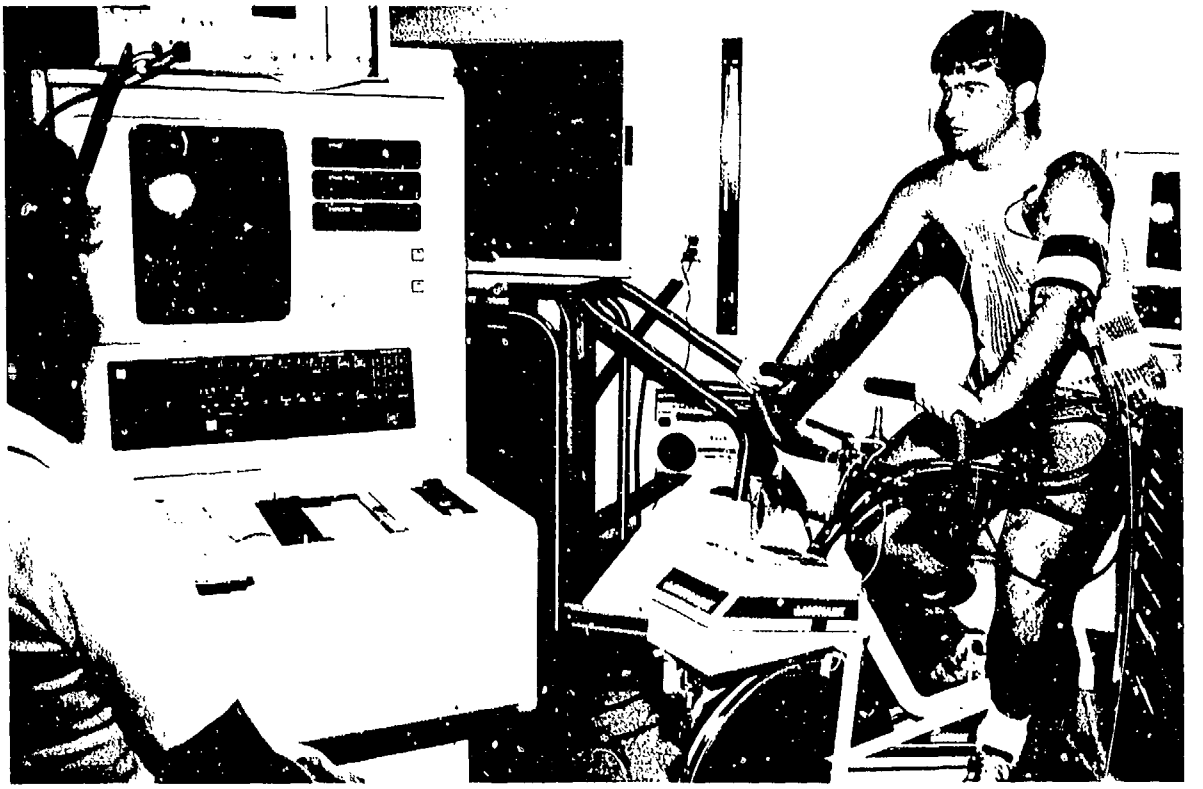

Fig. 7. Submaximal working capacity was evaluated using the Astrand Multi-Stage procedure on the bike ergometer.

Fig. 8. Dynamic strength and endurance was evaluated using the Cybex II Isokinetic Muscle Testing Equipment.

acceleration energy measured as work performed in the first 1/8 s of torque production, peak torque to body weight ratio, and endurance ratio measured as work accomplished in the last five repetitions (out of 50 repetitions at 180° per second) compared to work accomplished in the first five repetitions.

9. Pulmonary Function. A pulmonary function test (PFT) was administered using the calibrated Jaeger Pneumonscreen (Fig. 9) (72). The PFT measured forced expiratory volume at 1 s ($FEV_{1.0}$), forced vital capacity (FVC), forced expiratory flow at 50% total lung capacity (FEF-50), and maximal voluntary ventilation (MVV).

TEST SCHEDULE

Subjects were tested on consecutive Tuesday and Thursday evenings starting at 2000 hours. Tests were conducted before a sleep period and after a sleep period of approximately 4 h (Table 1). Half of the subjects received the drug on Tuesday; the remaining half received it on Thursday.

TABLE 1. Activity schedule (time (h) after drug administration)

Activity	Before sleep	After sleep
Drug administration	0	-
Interval prod. & matrix rot.	1	8.5
Balance, tracking & pegboard	1.5	9
Tilt table	2	9.5
Pulmonary function	2.5	10
Submaximal working capacity	3	10.5
Muscle strength & endurance	3.5	11
Sleep	4.5	-

Previous experience with the Cybex measures of strength/endurance and the two-dimensional tracking test indicated that several training periods would be needed to stabilize performance. During the 3 to 4 days preceding testing, each subject completed four 30-min sessions on the Cybex device and three 30-min sessions of tracking.

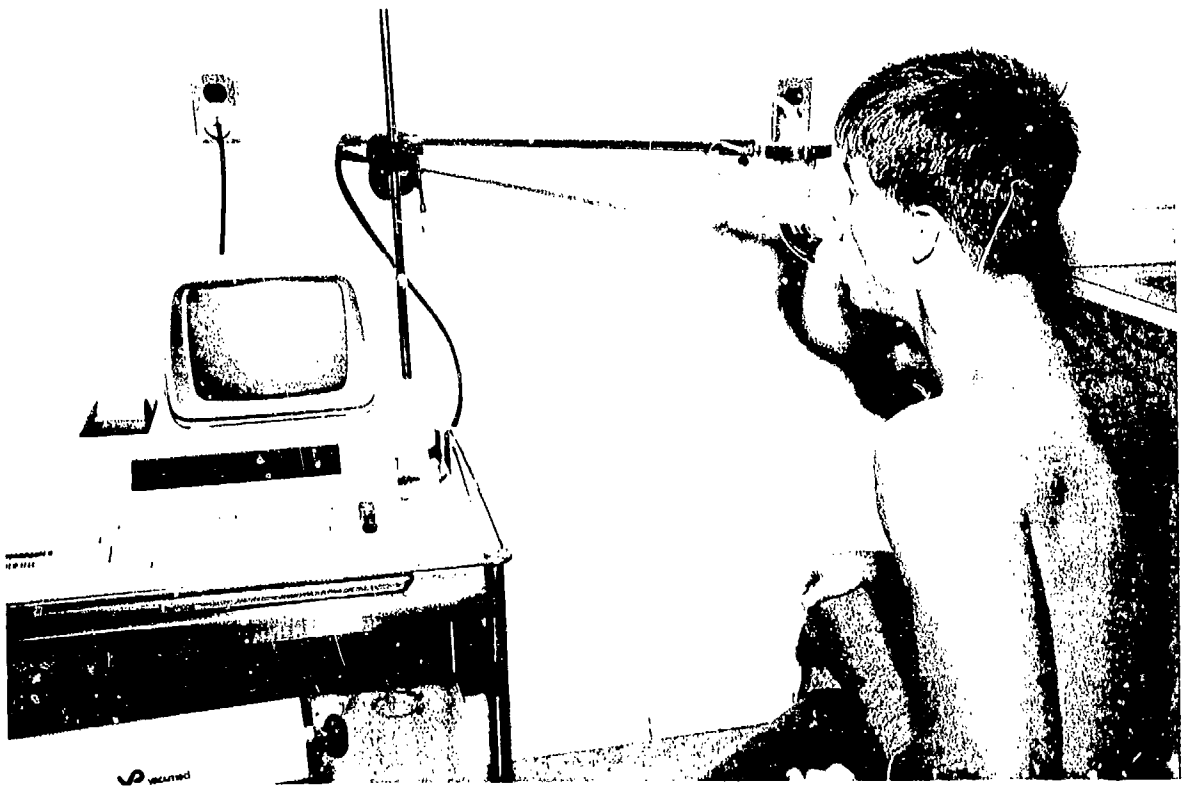

Fig. 9. The pulmonary function test (PFT) was administered using the calibrated Jaeger Pneumonscreen.

RESULTS

BALANCE

Sharpened Romberg

Triazolam significantly reduced static balance as measured by the Sharpened Romberg at both 1.5 h ($t = 2.24$, $df = 9$, $p < .05$) and 9 h ($t = 2.39$, $df = 9$, $p < .05$) following drug administration. Placebo testing at 1.5 h and 9 h did not significantly differ (Table 2). Triazolam testing at 1.5 h and 9 h did not significantly differ although variability was increased relative to placebo testing.

TABLE 2. Sharpened Romberg Data

Test condition	Time after drug administration (h)	Mean time (s) (± 1 SD)
Placebo	1.5	234.5 (11.65)
Placebo	9	231.8 (16.29)
Triazolam	1.5	184.1 (72.12)
Triazolam	9	178.6 (70.01)

Walk-on-Floor-Eyes-Closed (WOFEC)

Ambulatory balance at 1.5 h following triazolam administration was depressed and statistically different from the results obtained under drug at 9 h ($t = 3.16$, $df = 9$, $p < .05$). The triazolam versus placebo data at 1.5 h were not statistically different ($t = 1.94$, $df = 9$, $p =$ N.S.).

TABLE 3. WOFEC Data

Test condition	Time after drug administration (h)	Mean time (s) (± 1 SD)
Placebo	1.5	28.0 (5.01)
Placebo	9	28.2 (1.32)
Triazolam	1.5	24.9 (4.23)
Triazolam	9	29.3 (1.25)

INTERVAL PRODUCTION TASK

The primary dependent measure for this test was variability in tapping rate. The formula for calculating the variability score (V) follows:

$$V = \frac{N}{T} \sum_{i=1}^{N} \left| \Delta t_i \right|$$

where N is the total number of intervals produced, T is the total time over which data are collected, and t is the difference between successive intervals. A lower variability score indicates more temporally regular tapping and better performance. Typical variability scores range from 10 to 40.

Triazolam did not significantly alter variability scores (Table 4). Variability significantly increased during the post-sleep (8.5 h) resting period ($\underline{F}$ (1,9) = 9.64, $\underline{p}$ < .05).

TABLE 4. Variability Score Summary

Test condition	Time after drug administration (h)	Mean time (s) (± 1 SD)
Placebo	1	22.88 (7.63)
Placebo	8.5	24.79 (5.82)
Triazolam	1	22.07 (9.15)
Triazolam	8.5	25.50 (9.35)

MATRIX ROTATION TEST

Group summary data for the matrix rotation test are presented in Table 5. There were no statistically significant differences between any of the testing conditions.

TABLE 5. Matrix Rotation Test

Test condition	Time after drug administration (h)	Correct responses (%)	Mean reaction time (msec)
Placebo	1	88.86	1035
Placebo	8.5	90.09	1075
Triazolam	1	88.16	1052
Triazolam	8.5	89.33	1096

TILT TABLE TEST

Summary data for HR and BP responses to orthostatic tilts are presented in Table 6. Triazolam did not significantly change HR or BP responses although there was a tendency (statistically non significant) for HR to increase shortly after drug administration.

TABLE 6. Tilt Table

Variable	Test condition	Time after drug administration (h)	Mean response for designated testing interval (min)		
			1-5	6-20	21-25
Heart rate	Placebo	2	60.9(9.3)	79.1(11.8)	59.0(10.5)
	Placebo	9.5	59.8(10.0)	78.0(8.1)	57.9(9.6)
	Triazolam	2	65.3(9.9)	86.6(13.8)	61.0(11.7)
	Triazolam	9.5	60.3(8.1)	82.4(9.8)	57.9(10.5)
Diastolic BP	Placebo	2	64.4(12.6)	79.2(11.1)	64.3(13.0)
	Placebo	9.5	65.1(5.6)	77.1(7.2)	63.1(6.6)
	Triazolam	2	64.0(11.4)	78.9(9.6)	62.3(10.2)
	Triazolam	9.5	63.6(6.3)	77.9(6.7)	62.2(6.2)
Systolic BP	Placebo	2	117.8(13.6)	118.6(11.6)	116.8(12.3)
	Placebo	9.5	113.5(12.4)	114.9(9.9)	112.6(11.5)
	Triazolam	2	114.8(12.4)	115.7(10.5)	113.4(12.9)
	Triazolam	9.5	112.2(8.9)	113.5(8.7)	111.3(9.8)

PEGBOARD TESTS

Results of the Pegboard Test are summarized in Table 7. For the placebo testing condition, both right- and left-hand responses were significantly faster at 1.5 h versus 9 h (t = 2.8 and 2.05, respectively; df = 9, $p < .05$). None of the other comparisons was significantly different.

TABLE 7. Pegboard Test

Test condition	Time after drug administration (h)	Mean response time in seconds (± 1 SD)	
		Right hand	Left hand
Placebo	1.5	56.6(5.1)	64.4(11.3)
Placebo	9	61.6(6.8)	69.3(12.8)
Triazolam	1.5	60.3(9.4)	65.1(8.4)
Triazolam	9	61.0(8.0)	68.4(14.8)

TRACKING

Equipment failure limited the collection of data on this task to six subjects. Due to the similarity of results, the pitch- and roll-axis error data have been combined and presented as a single error score (Table 8). The only statistically significant change was an improvement in tracking as the horizon length was increased ($F(3,15) = 20.03$, $p < .001$).

TABLE 8. Combined Pitch and Roll rms Tracking Error (Volts)

Test condition	Time after drug administration (h)	Mean rms error (± 1 SD) by horizon length			
		3.9°	9°	16°	30°
Placebo	1.5	518(43)	430(45)	401(22)	385(46)
Placebo	9	535(98)	470(76)	450(67)	408(50)
Triazolam	1.5	534(56)	453(72)	422(52)	402(27)
Triazolam	9	600(164)	502(120)	460(58)	460(78)

SUBMAXIMAL WORKING CAPACITY TEST (PWC_{150})

Triazolam had no significant effect on either predicted VO_2 max (Table 9) or total work (Table 10).

TABLE 9. Predicted VO_2 max ml/kg from PWC_{150}

Test condition	Time after drug administration (h)	Mean (± 1 SD)
Placebo	3	3.42(.67)
Placebo	10.5	3.53(.80)
Triazolam	3	3.27(.56)
Triazolam	10.5	3.46(.82)

TABLE 10. Total Work on the PWC_{150} Test (joules)

Test condition	Time after drug administration (h)	Mean (± 1 SD)
Placebo	3	10686.3(5184.5)
Placebo	10.5	10595.9(3936.2)
Triazolam	3	9574.8(4888.8)
Triazolam	10.5	9768.9(5221.0)

MUSCULAR STRENGTH AND ENDURANCE

No statistically significant differences were seen in any of the muscular strength and endurance parameters (Tables 11 and 12, respectively).

TABLE 11. Muscular Strength (Mean ± 1 SD, 60° per second)

Test condition	Time after drug administration (h)	Total work units extension	Total work units flexion	Average power units extension	Average power units flexion	Peak torque units extension	Peak torque units flexion
Placebo	3.5	700.0 (182.1)	577.6 (136.7)	106.8 (30.2)	79.6 (18.0)	137.6 (46.0)	112.1 (22.4)
Placebo	11	709.5 (140.6)	606.3 (167.6)	104.8 (22.2)	81.8 (22.6)	121.6 (43.2)	109.2 (26.6)
Triazolam	3.5	703.8 (150.3)	575.4 (129.2)	109.3 (21.7)	78.6 (17.5)	121.2 (44.3)	105.7 (21.5)
Triazolam	11	734.9 (172.3)	582.0 (159.6)	103.5 (24.0)	76.7 (20.3)	130.9 (37.2)	110.4 (24.9)

TABLE 12. Muscular Endurance (Mean ± 1 SD, 180° per second)

Test condition	Time after drug administration (h)	Total work units extension	Total work units flexion	Average power units extension	Average power units flexion	Endurance ratio units extension	Endurance ratio units flexion
Placebo	3.5	3230.8 (848.2)	2354.7 (612.8)	123.2 (39.1)	93.2 (24.2)	26.6 (16.4)	32.0 (16.7)
Placebo	11	3058.9 (825.2)	2292.6 (709.4)	119.9 (29.2)	89.2 (26.2)	25.9 (10.2)	31.2 (14.6)
Triazolam	3.5	3200.5 (839.3)	2262.9 (669.1)	129.7 (33.9)	91.5 (30.0)	26.7 (11.7)	40.1 (12.7)
Triazolam	11	3158.7 (837.8)	2277.6 (720.1)	124.6 (31.5)	89.2 (29.0)	27.2 (10.3)	39.4 (30.4)

PULMONARY FUNCTION

No statistically significant results were seen for any of the pulmonary function measures ($FEV_{1.0}$, FVC, FEF-50, and MVV; Table 13).

TABLE 13. Summary Table of Pulmonary Function Tests (Mean ± 1 SD)

Test condition	Time after drug administration (h)	$FEV_{1.0}$	FVC	FEF-50	MVV
Placebo	2.5	4.24 (0.53)	5.48 (.91)	4.81 (1.36)	11.97 (2.47)
Placebo	10.0	4.37 (0.70)	5.52 (1.00)	4.98 (1.42)	12.09 (2.40)
Triazolam	2.5	4.32 (0.69)	5.44 (1.04)	4.89 (1.30)	12.31 (2.63)
Triazolam	10.0	4.40 (0.63)	5.57 (1.02)	5.22 (1.34)	12.34 (2.85)

DISCUSSION

Vestibular, musculoskeletal, and complex performance as measured in this study were generally not affected by this dose (0.25 mg) of triazolam. Many of the subjects could not distinguish the drug versus the placebo conditions even though the initial testing was during the peak drug effect (1 to 4.5 h following administration). The marginally significant decrements in balance associated with triazolam should be evaluated with caution considering the gross nature of the test and the marginal significance ($p < .05$). We recommend that a more sophisticated measure of balance (i.e., force-balance platform) be used to clarify these initial observations.

The operational military community is concerned with the possibility of a drug-induced hangover and an associated performance decrement following the assisted sleep period. As previously stated, within the confines of our test battery, we did not encounter performance decrements in the 'after sleep' test sequence (8.5 to 11.5 h post drug). This result, combined with the lack of performance effects during the control or peak drug effect period (1 to 4.5 h post drug), suggests that a single dose of 0.25 mg triazolam has either no or very mild effects on performance. This possibility is supported by anecdotal reports from our subjects indicating difficulty distinguishing drug and placebo conditions and similar reports from RAF pilots using the related compound temazepam. This interpretation should be tempered by the fact that performance testing was limited to the tests described. The reader may want to review other literature relative to triazolam's influence on psychological functions (3,5,52,53,62,68,84) and vision (78,84). The influence of triazolam on visual and auditory functions is currently being evaluated in our laboratory. An alternate possibility is that our tests were insensitive to drug-induced changes. This possibility is supported by the lack of performance decrements during the peak drug-effect period. We recommend that future studies include drugs that can confirm test sensitivity.

The results from this study did not identify any significant performance side effects that would disqualify this agent (0.25 mg triazolam) for

acute/short-term use against insomnia, which is sometimes encountered in the military aviation environment. The general lack of a drug effect was somewhat surprising in light of the fact that during 'pilot' tests, three subjects taking 0.5 mg triazolam experienced prolonged impairment, which would have been detrimental from an operational standpoint. This effect might have been an idiosyncratic reaction, or it might have reflected a strong dose-response reaction. We recommend that before this agent is used in an operational scenario, aviators should be screened by a drug challenge to identify any idiosyncratic reactions. Additional research on dose-response effects may be warranted.

CONCLUSIONS

This dose of triazolam (0.25 mg) produced no significant change in any of the tests with the exception of the balance tests ($p < .05$). Within the confines of our test battery, we did not identify any significant performance side effects that would disqualify 0.25 mg triazolam for acute/short-term use against insomnia sometimes encountered in the military aviation environment.

RECOMMENDATIONS

We recommend: (1) a more sensitive balance test be used in future investigations; (2) potential changes in psychological and vision functions be explored; (3) future studies should include control drug(s) to confirm test sensitivity; (4) before using this agent in an operational scenario, aviators should be screened by a drug challenge to identify any idiosyncratic reactions; and (5) additional research on dose-response effects be conducted.

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